Remarks

Applicants submit the following amendments and remarks in response to the office action and restriction requirement mailed on March 13, 2006, setting a period for response expiring June 13, 2006. Accordingly, this response is timely filed. If there is any other fee due, the Office is authorized to charge Deposit Account No. 500239.

Claims 20-24 are pending in this application.

Priority and IDS

Applicants thank the Examiner for acknowledging that this application claims benefit of 60/399,491, filed on 07/29/2002 as well as claiming benefit under 35 U.S.C. 119(a)-(d) to application no. 0216515.7 filed in the United Kingdom Patent Office on 07/06/2002, which papers have been placed of record in the file.

Applicants thank the Examiner for considering the IDS filed on 09/02/2003.

Election/Restrictions

Applicants thank the Examiner for her decision to rejoin Group II with Group I and search Claims 20-23 directed to the products of fosfluconazole. Applicants acknowledge that Claim 24 directed to the process of making the fosfluconazole will not be examined at this point in the examination process, but if the claimed products are allowable, the process of making this product (Claim 24) will be rejoined.

Double Patenting Rejection

Claims 20-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 2 of U.S. Patent Num. 6,977,302 ('302 Patent). '302 Patent Claim 2 teaches a compound which is: alkali metal salt of 2-(2,4-difluorophenyl)-1,3-bis(lH-1,2,4-triazol-1-yl)-2-propyl dihydrogen phosphate (i.e. fosfluconazole) (i.e. fosfluconazole). The Examiner stated that

> "The difference between '302 Patent and the instantly claimed compounds is that '302 Patent discloses an alkali metal salt (i.e. lithium, sodium, potassium, rubidium, cesium, francium) of fosfluconazole, while the instantly claimed compounds claim sodium only with specific water weights of the mixtures.... Although the conflicting claims are not identical, they are not patentably distinct from each other. The '302 Patent claims alkali metal salts, but the working examples in the specification are all directed to the disodium salts of fosfluconazole. The '302 Patent does not disclose specific water weight, but an absence of the water weight does not mean that it is different from the instantly claimed
> compound. Rather, one can assume that disodium salts of the '302 Patent are inherently the same as the disodium salts claimed in the instant application and would therefore have the same water weight. Generally, specific water weights of a salt of a known compound are not a good measure of patentability as water weight can change based on the level of impurity, water in the compound, humidity in the air, etc.... Applicant did not provide any data in the specification, which demonstrates that the instantly claimed disodium compound is not obvious over the compound in the '302 Patent. Therefore, one skilled in the art would have found this variation obvious when faced with '302 Patent because both compounds claim the same disodium salt of fosfluconazole, so one skilled in the art would expect similar properties and results."

For the reasons below, Applicants respectfully traverse. Applicants submit that the hydrate mix of a compound could, in principle, be controlled by a process which controls the Relative Humidity (RH) to which the compound is exposed. Such a process would comprise subjecting the compound or composition to a standard drying cycle in a freeze-drying apparatus followed by rehydration by providing a gas having an appropriately selected RH at a controlled temperature. However, in practice there would be a multitude of significant problems associated with such a process. Firstly, it is vital that compounds and compositions are prepared in sterile form when they are to be used for pharmaceutical purposes. This results in the significant practical problem of ensuring that the moist rehydration gas does not lead to corrosion or microbial contamination of the associated delivery system, which would severely impact on the economic viability of such a process. Furthermore, the rate of rehydration of the intermediate might not be sufficiently high to afford an economically viable process. In addition, it is possible that the compound or composition would be dried to the point that an unstable intermediate might be formed, which would mean that the end product of the process would be contaminated and therefore unacceptable for pharmaceutical use. The apparent instability of compounds having a mixture of unstable and stable hydration states (e.g. the compound disodium salt of fosfluconazole (hereinafter DSFF) as a mixture of mono- and tri-hydrates) limits their potential utility as drugs owing to poor shelf life and there is a need in the art, therefore, for a process of producing a stable hydrate mix of such compounds. In particular there is a need in the art for a process for producing a mixture of the tri-and hexahydrate forms of DSFF.

Surprisingly, the present inventors have now found that a compound having a mixture of unstable and stable hydration states can be treated by the process of the current invention to provide a corresponding hydrate mix which is both chemically and thermally stable and can be prepared in a reproducibly facile and economically viable manner. The present invention provides a process for the preparation of a stable hydrate mix of a compound, or a composition comprising the compound, the compound being capable of forming a plurality of hydration forms of differing stability and of dissolution to give a solution that, when frozen below the eutectic point, is a eutectic mixture, comprising (see specification as filed, page 4, line 17, to page 5, line 4):

a) providing a quantity of an aqueous mixture containing the compound or composition thereof in a suitable vessel in a freeze-drying apparatus;

b) reducing the temperature in the apparatus to bring about freezing and eutectic solidification;

c) reducing the pressure in the apparatus to below the saturation vapour pressure (SVP) of water over ice at the temperature of the ice;

d) maintaining the apparatus at a pressure below the SVP and, optionally, increasing the temperature in the apparatus to facilitate sublimation, until all of the ice has been sublimed;

e) maintaining the apparatus at the pressure and temperature conditions according to step d) until the desired water content has been obtained; and

f) either:

increasing the pressure in the apparatus to from about 60% to about 100% of atmospheric pressure (about 60.8 kPa to about 101.3 kPa) and subsequently adjusting the temperature in the apparatus to from about 5°C to about 30°C;

Or

adjusting the temperature in the apparatus to from about 5°C to about 30°C and subsequently increasing the pressure in the apparatus to from about 60% to about 100% of atmospheric pressure (about 60.8 kPa to about 101.3 kPa).

In testing the above process for the preparation of a stable hydrate mix of a compound or compositions thereof, the present inventors have found that some compounds, and compositions thereof, more particularly those exhibiting a plurality of hydration forms of differing stability, may be deleteriously affected by being subjected to the abovea secondary drying phase. In summary, the present inventors have found that, when exposed to the above process, the following tabulated data are provided (see page 3, lines 13-24 of the specification as filed):

DSFF product water content	Possible DSFF hydrate form	Stability
about 1.2% w/w (below 4.0% w/w water)	below its monohydrate stoichiometry	unstable and degrades
from 4.0% w/w to 11.2% w/w	combination of tri- and monohydrate forms	unstable
Above 20.1% w/w	above the hexahydrate stoichiometry (20.1% w/w), such as dodecahydrate (33.4% w/w water)	collapse

In the specification as filed, the present inventors have provided examples of DSFF that are stable and therefore enable the compounds and compositions to be prepared in sterile form when they are to be used for pharmaceutical purposes, such as longer shelf life. The data provided in the specification examples 1-6 as tabulated below:

Example # and page #	DSFF product water content/hydrate form	Stability
Example 1, page 7 of the specification	mean water content of 11.7 % w/w	stable
Example 2, page 8 of the specification	14.6 % w/w	stable
Example 3, page 8 of the specification	16.9 % w/w	stable
Example 4, page 10 of the specification	a mixture of tri- and hexahydrate forms of DSFF	chemically and thermally stable
Example 5, page 10 of the specification	DSFF trihydrate (about 11% w/w)	stable
Example 6, page 10 of the specification	DSFF hexahydrate (about 20% w/w)	stable

Based on the above exemplified data, the present inventors found that the preferred final water content of the stable hydrate mix of DSFF is from about 11% to about 20% w/w, more preferably, from about 14% to about 17% w/w, most preferably from about 15% to about 16% w/w, such as about 15 %, as recited in the above claims 20-23. The DSFF hydrate or hydrate mix of the present invention have chemically and thermally stable, and have a high degree of crystallinity.

As to claim 2 of the '302 Patent cited by the Examiner, Applicants respectfully submit that the claim recites the alkali metal salt of 2-(2,4-difluorophenyl)-1,3-bis(lH-1,2,4-triazol-1-yl)-2-propyl dihydrogen phosphate (i.e. fosfluconazole) having no particular water content. The alkali metal salt of the claim 2 of the '302 Patent was not subjected to the present process of the invention for the preparation of a stable hydrate mix of a compound or compositions thereof. Based on the teaching of the '302, those skilled in the art would not have been motivated to prepare the specific DSFF hydrates or mixtures thereof that are stable for making pharmaceutical compositions containing DSFF. Further, based on the teaching of the '302 Patent those skilled in the art would not have been motivated to control the DSFF composition water content that would provide DSFF hydrates or mixtures thereof that are stable in order to provide a corresponding DSFF hydrate mix which is both chemically and thermally stable and can be prepared in a reproducibly facile and economically viable manner. Thus Applicants respectfully submit that claim 2 of the '302 Patent does not teach or provide motivation to provide the stable DSFF trihydrate, stable DSFF hexahydrate, or stable mixture thereof having the specific water content as claimed in the present invention.

Based on the above arguments, Applicants respectfully request that the Examiner remove the obviousness double patenting rejection, allow the present product claims 20-23, and rejoin and allow the product by process claim 24.

Respectfully submitted,

Date: June 12, 2006

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